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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,240	10/19/2001	Johan Weigelt	13425-047001	5027
26161	7590	05/04/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			DAVIS, DEBORAH A	
			ART UNIT	PAPER NUMBER
			1641	
DATE MAILED: 05/04/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/986,240

Applicant(s)

WEIGELT ET AL.

Examiner

Deborah A Davis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2-9-04.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, -10 and 12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's response to the Office Action mailed November 6, 2003 is acknowledged. Currently, claims 1-10 and 12 are pending and under consideration. Claim 11 is cancelled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1, 4-5, 8-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al (Journal of Biomolecular NMR, 11: 1998) in view of Graham J. Moore (USP#6,060,603).

Yabuki et al teaches a method for stable-isotope labeling of proteins by cell free synthesis. In this method, a technique that utilizes Ras protein samples in which the main chain carbonyl carbons of one amino acid type (AA1) are labeled with ^{13}C carbons and another amino acid type (AA2) is labeled with ^{15}N are evaluated with HNCO-type NMR and 2D1-H-15N NMR (see NMR measurements, pg 299 and pg. 300, Figure 1). The amino acid Ser³⁹ (AA2) occurs directly subsequent to Asp³⁸ (AA1) as recited in claim 1 (pg. 301, paragraph 1). Yabuki et al evaluates several amino acid labeled pairs by NMR techniques; such as, the amino acids Asp and Ser are labeled in a pair located within the Ras protein (pg. 300, paragraphs 1 and 2). The labeled Ras protein was then complexed with the binder protein Raf RBD, and evaluated with NMR HNCO spectrum

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and then compared with the results of the NMR spectrum of labeled amino acid pairs (pg. 301, paragraph 1 and pg 302, Figure 3). Chemical shift differences such as cross peaks of labeled amino acid pairs of the Ras protein were observed, compared, recorded both by itself and complexed with the Raf RBD, indicating interaction between the labeled Ras protein and the Raf protein complexed with the binding protein as recited in claim 1 (pg. 300, last paragraph and pg. 301, first paragraph). The Ras-Raf RBD complex has a molecular mass of about 30 kDa as recited in claim 8 (pg. 300, last paragraph). The reference points out that labeled amino acid pair, Pro-Thr is unique in the Ras protein and was identified by the HNCO experiments as recited in claims 4 and 5 (pg. 300, paragraph 5, lines 17-19). This dual labeling technique can be performed on very large proteins with a molecular mass of about 150 kDa (pg. 296, paragraph 2). Thus, dual labeling and site-directed labeling by cell-free protein synthesis will be useful techniques for analyzing the structures of proteins as recited in claim 12 (pg. 305, last paragraph, last 3 lines).

Yabuki et al does not teach that the potential binder molecule has a molecular mass from 50-1000 Da.

However, Graham J. Moore teaches the use of NMR techniques which are employed to evaluate tertiary structures of biological active ligands that has a molecular weight of < 500 or > 2000 Daltons (col. 3, lines 1-46) and also includes through-bond coupling patterns within a molecule (col. 13, lines 22-50). Preferably, when analyzing by NMR, the ligand should have a molecular weight of less than 3,000 Daltons.

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It would have been obvious to one of ordinary skill in the art to modify the teachings of Yabuki et al to include the use of small molecular weight ligands to evaluate tertiary structures of biological active ligands as taught by Graham J. Moore. Further, absent evidence to the contrary, the range recited in the instant claims from 50-1000 Daltons is viewed as mere optimization of the prior art assay.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 2-3 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al in view of Graham J. Moore and in further view of Fesik et al (WO97/18471)

The teachings of Yabuki et al and Graham J. Moore are set forth above and differ from the instant claims by not teaching the sphere radius of the labeled amino acid pair, the proximity of an active site within the protein, neither does Yabuki mention the result of the above described method is compared to the result of any other binding or activity assay.

However, Fesik et al teaches a method for identifying ligands which bind to a specific target molecule labeled with radioactive isotopes and said ligand binding is evaluated by NMR. Studies were also performed to compare binding constants of

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ligands to various biomolecules, determined by the NMR method, such as enzymatic, filter binding and gel shift screening assays (pg. 26, lines 18-24 and pg. 27, lines 1-9).

An advantage of using NMR in screening assays is the ability to correlate observed chemical shifts from two-dimensional NMR correlation spectra with other spectra projections of target molecule configuration (pg. 24, lines 1-14).

It would have been obvious to one of ordinary skill in the art to incorporate a comparison method of the various assays as taught by Fesik et al into the method of Yabuki et al in view of Graham J. Moore to compare the binding of ligands to various biomolecules determined by NMR and to also observe chemical shifts from observed by 2-D NMR techniques. With respect to claims 2, 3 and 6, one skilled in the art would recognized that the proximity and spatial orientations of amino acids within a protein can be modified in such a way to get the desired results, especially since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

Response to Arguments

6. Applicant's argues that the reference of Yabuki is not concerned with using the labeling technique to screen for an identify a molecule that binds to a given protein, therefore, the skilled artisan would have not reason to modify the methods of Yabuki with the reference of Moore to test candidate compounds for their ability to bind to Ras or any other protein.

This argument is noted but is not found persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, Yabuki could identify a binder molecule such as Raf by investigating the structure of the proteins and also by the comparison of NMR spectra that exhibited a signal change when the Ras and Raf protein formed a binding complex. Although applicant contends that the instant invention use potential binders in a screening protocol, the Raf binding protein taught by Yabuki is considered to be a potential binder until binding is actually detected. Therefore, the reference of Yabuki can be modified with the reference of Moore et al to make obvious the instant invention taught by applicant.

7. Applicant argues that none of the references of record describe a low molecular weight compound (i.e., having a molecular mass of 50 to 1000Da) that was known to bind to Ras that the skilled artisan might have attempted to use in the method of Yabuki in place of Raf to investigate the nature of Ras-ligand interaction. Applicant further argues that because Yabuki didn't describe a screening assay for potential binder molecules, there would not have been a basis or rationale for a skilled artisan to optimize the methods by replacing Raf (a known ligand of Ras) with a molecule having a molecular mass of 50 to 1000Da.

Applicant's argument is noted but not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Moore et al teaches proteins with molecular weights that meet the limitation of 50 to 1000Da and the advantages of using them in NMR screening (see col. 13, lines 22-50). In addition, the reference of Moore was also concerned with evaluating tertiary structures of biological ligands (see motivational statement above), therefore, the references of Yabuki and Moore et al are combinable.

8. Applicant argue that nothing in Yabuki suggests generating the two NMR spectra recited in the claims and comparing the two spectra to identify and interaction between a potential binder molecule having a mass of from 50-1000Da and a labeled polypeptide.

Applicant's argument is noted but not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Yabuki taught that in addition to analyzing protein structures, the instant reference was also useful in analyzing protein-protein interaction (see page 305, column 2, last paragraph). This protein-protein interaction was analyzed by comparing Ras in

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bound form to Ras and Raf binding (see page 301, paragraph 1, and page 302, Figure 3). As noted above, Moore et al discloses analyzing proteins using NMR with a molecular mass of 50-1000Da and the advantages of using them. Therefore, it is the Examiner's position that Yabuki in view of Moore et al do render obvious the instant claim 1.

9. Applicant argues that the WO 97/18471 reference does not add to the reference of Yabuki and Moore et al because this instant reference teaches a process of identifying compounds with a potential binder versus Yabuki that teaches analyzing structures of proteins.

This argument is noted but not found persuasive because the Raf binding protein taught by Yabuki is considered to be a potential binder until binding is actually detected and identified. Therefore, based on the arguments aforementioned above, the instant rejection is maintained and made final.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 29, 2004


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05/01/04